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Distal Arthrogryposis Type 1: Clinical Analysis of a Large Kindred

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We describe the clinical findings of 15 individuals in a large kindred affected with distal arthrogryposis type 1A (DA1A). The most consistent findings among individuals were overlapping fingers at birth, abnormal digital flexion creases, and foot deformities, including talipes equinovarus and vertical talus. There was marked intrafamilial variation in the expression of DA1A. Linkage mapping of the locus for DA1A suggests that the use of strict diagnostic criteria excludes unaffected individuals rigorously, but can produce incomplete ascertainment of affected individuals. In the context of an affected family, the range of phenotypes consistent with a diagnosis of DA1A needs to be expanded. © 1996 Wiley-Liss, Inc.

KEY WORDS: distal arthrogryposis, contractures, club foot

INTRODUCTION

The prevalence at birth of any type of congenital contracture is 0.5–1.0%, and over 150 conditions have been described in which multiple congenital contractures may be present [Hall, 1985]. The most common reported congenital contractures are dislocated hips (0.5%) and club feet (0.2%) [Hall et al., 1982]. A child with multiple congenital contractures is identified in 1 of every 3,000 births [Hall et al., 1982]. The term *arthrogryposis* describes individuals with nonprogressive congenital contractures of two or more different body areas. Amyoplasia is probably the most common condition referred to as "classical arthrogryposis" in the medical literature and by orthopedists [Hall et al., 1982].

The distal arthrogryposes (DAs) constitute the second largest group of disorders distinguished by multiple congenital contractures. DA is defined as an inherited primary limb malformation disorder characterized by congenital contractures of two or more different distal body areas and without primary neurologic and/or muscle disease that affects limb function [Bamshad et al., in press]. Hall et al. [1982] divided the DAs into two different groups, DAI and DAII. Following the introduction of this nomenclature, reports emphasizing the overlapping distributions of physical traits among different DAs as well as new conditions characterized by distal contractures were published [Kawira and Bender, 1985; Reiss and Sheffield, 1986; Moore and Weaver, 1989; Chitayat et al., 1990; Schrander-Stumpel et al., 1991; Lai et al., 1991; Klemp and Hall, 1995]. This has led to a proposed revision and extension of the Hall et al. [1982] DA classification, in which nine distinct inherited DA disorders are categorized [Bamshad et al., 1996].

DA1 (formerly DAI; OMIM 108120) is a highly penetrant autosomal dominant disorder characterized in large part by congenital flexion contractures of two or more different distal body areas and no additional anomalies [Hall et al., 1982; Hall, 1985, 1989, 1992]. The prevalence of DA1 is approximately 1 in 10,000 to 1 in 50,000 [Bamshad et al., 1994], and it is a common cause of inherited club foot. Two groups of patients with DA1 are recognized in the revised classification of DA disorders, although they cannot be distinguished from each other clinically. DA1A is diagnosed by determining whether the allele segregating in a family affected with DA1 maps to chromosome 9 [Bamshad et al., 1994]. DA1 families not mapping to chromosome 9 are tentatively labeled with DA1B.

Most individuals affected with DA1 demonstrate flexion contractures at birth. The most frequently affected joints are the hands (98%) and the feet (88%) [Hall et al., 1982]. The hands are typically held in a characteristic position consisting of a tight fist with medial overlapping of the fingers and an adducted thumb. Approximately 40% of affected individuals have an equinovarus deformity of one or both feet. Neurologic exams are normal, and intelligence is unaffected. There is marked intra- and interfamilial variability in the severity of expression. As affected children begin to ex-

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ercise, their hands can become quite functional. Affected adults may demonstrate residual camptodactyly and/or ulnar deviation of the fingers at the metacarpal phalangeal joint. Twenty percent of affected adults have straight and fully functional fingers. Hence, absent distal interphalangeal creases may be the only residual finding in the upper limbs. Overlapping of the toes may be the only residual manifestation in the feet. The pathogenic mechanisms responsible for DA1 have yet to be defined. Misplaced, hypoplastic, or absent tendons have been documented in some patients [Hall et al., 1982].

This paper describes the range of phenotypic variation observed in a kindred having 15 individuals affected with DA1A.

CLINICAL REPORTS

All studies were performed with the approval of the institutional review board of the University of Utah and the general counsel of the Shriner's Hospitals for Crippled Children. Fourteen affected individuals and their relatives in an extended Utah kindred (Fig. 1) were evaluated by interview and physical examination. One relative was deceased and could not be evaluated directly. Their ancestors were former members of the "Pennsylvania Dutch" and subsequently of the original Mormon pioneers who settled in Utah in the 19th century. There is no history of consanguinity.

An individual was diagnosed as affected on the basis of a family history and the presence of one or more of the major diagnostic criteria of DA [Bamshad et al., 1996]. Major diagnostic traits of the upper limbs included overriding fingers at birth, absent or hypoplastic digital flexion creases, camptodactyly, and/or ulnar deviation. Major diagnostic traits of the lower limbs included metatarsus varus, talipes equinovarus, a vertical talus, and/or a calcaneovalgus deformity.

No abnormalities of amniotic fluid volume or umbilical cord length were noted. There were no consistent complications of pregnancy or delivery. All affected individuals had normal intelligence. No affected individuals had short stature, blepharophimosis, ophthalmoplegia, a cleft lip or palate, micrognathia, retrognathia, or scoliosis. The most consistent diagnostic characteristics were overlapping fingers at birth, abnormalities of the digital flexion creases, and positional foot deformities (Table I). Camptodactyly and ulnar deviation were also common. There was no evidence of genetic anticipation. There did appear to be a parent-of-origin effect and/or familial clustering of anomalies. That is, the children of the only affected female to reproduce appeared to be consistently more severely affected than the children of affected males. Additional families will be studied to verify whether there is indeed a parent-of-origin effect.

The severity of phenotypic expression varied from limited range of motion at the shoulders as well as small calves (without an associated positional foot deformity) in individual II-4 to overlapping fingers, camptodactyly, abnormal flexion creases, ulnar deviation, bilateral talipes equinovarus, and bilateral dislocated hips in individual IV-6. A mild limitation in opening of the mouth was observed in 5 individuals (III-5, III-6, III-13, IV-7, and IV-16). These individuals did not have an abnormally shaped mouth, or unusual skin folds and/or dimpling around the mouth. There was no apparent association in the severity of expression between parent and child, nor was disease severity associated with the sex of the affected individual.

Individual I-1 had bilateral talipes equinovarus that was never corrected. He required "specially fitted" footwear that essentially enabled him to walk with severely internally rotated and plantar-flexed feet. Management of all other affected relatives included stretching exercises, serial casting, and/or surgical intervention. All affected relatives are ambulatory without "assist" devices. Most relatives in generation III received prenatal counseling to explain the risk of

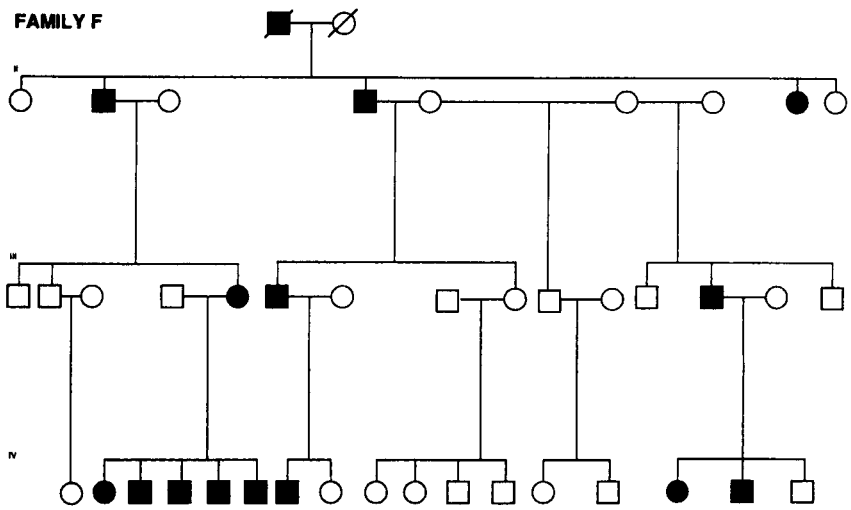

Fig. 1. Pedigree of family with DA1A. Affected individuals are denoted by a filled symbol, unaffected by an open symbol.

TABLE I. Summary of Manifestations*

Subject	Major diagnostic criteria					Minor diagnostic criteria
	Overlapping fingers	Hypoplastic/ absent flexion creases	Camptodactyly	Ulnar deviation	Positional foot deformities	
II-2	X	X		X		LROM
II-4						LROM Small calves
II-8	X	X	X	X	TE	
III-5	X	X	X	X	TE	Small mouth
III-6	X	X				LROM Small mouth
III-13	X	X				LROM Small mouth
IV-2	X	X	X		TE	
IV-3	X	X	X		TE	
IV-4	X	X	X	X	TE	
IV-5	X	X		X	TE	Hip dislocation
IV-6	X	X	X	X	TE	Hip dislocation
IV-7	X	X		X	TE	Small mouth
IV-15	X					LROM
IV-16	X			X	VT	LROM Small mouth
I-1[a]	X				TE	

* TE, talipes equinovarus; VT, vertical talus; LROM, limited range of motion.
[a] Deceased, clinical information obtained from photographs and interviews of descendants.

transmitting DA1A to their descendants. None of these individuals elected to alter their family planning. At least one affected individual who did not receive counseling elected not to reproduce because of the risk of having affected children. Prenatal diagnosis of DA1A was made by uterine sonographic examination in one pregnancy.

DISCUSSION

The broad distribution of anomalies among affected individuals in this kindred illustrates the highly variable expression of DA1A. Since DA1A is presumably caused by the same disease allele in each affected individual in this family, such variability suggests that the phenotype is influenced by genetic and environmental variables (e.g., uterine malformations, quantity of amniotic fluid) that partly control distal limb growth, development, and positioning. The existence of such modifiers is further supported by the apparent clustering of abnormalities among affected sibs which presumably share a more common environment as well as genetic background. Although reduced penetrance in females has been suggested in some DA families [Ioan et al., 1993], penetrance appeared equal between males and females in this kindred. These observations will have to be confirmed in additional DA1A families before they can be considered general characteristics of this disorder.

In the clinical summaries of Hall et al. [1982], the expression of DA1 was predominately in the distal limbs, and contractures were *always* present at birth, although in two families the parent was "so mildly affected that only in retrospect and with careful questioning was he or she recognized to carry the gene." The most mildly affected individual in this kindred (II-4) did not have contractures at birth, nor did he have abnormal digital flexion creases. In fact, it is likely that he would have been considered unaffected outside the context of his family (he was an obligate carrier). Individual IV-15 (affected) had overlapping fingers at birth but no additional major diagnostic traits, although she has limited range of motion of her popliteal joints.

Klemp and Hall [1995] have suggested that the penetrance of DA1 in the Maori population may be as low as 60–80%, although confirmation awaits identification of at least one locus causing DA1 in the Maori. It does not appear that the penetrance of DA1A is that low in Caucasians as our conservative estimate is 93% using strict diagnostic criteria to define affected individuals: 1 of 14 affected individuals we examined do not meet the diagnostic criteria for a DA disorder. However, all individuals in this kindred with the DA1A haplotype, including the 2 individuals who could be considered non-penetrant, have congenital musculoskeletal abnormalities [Bamshad et al., 1994]. This suggests that in the context of a family history of DA1A, findings in addition to those considered major diagnostic criteria could be considered disease traits.

We propose to expand the diagnostic criteria for DA1A to include a group of minor anomalies that may facilitate complete ascertainment without generating incorrect diagnoses. These minor diagnostic criteria include limited range of motion of the proximal joints, congenital hip dislocation, small calves, and a mildly limited opening of the mouth. In the context of a family history of DA1A, an individual would be considered affected in the presence of one major or two minor diagnostic criteria. Without a positive family history of

DA1A, two major diagnostic criteria would have to be present to tentatively diagnose an individual as affected because differentiation between other causes of multiple distal limb contractures, including other DA disorders, and DA1A is often not possible.

A small mouth, scoliosis, short stature, ophthalmoplegia, hearing loss, and the presence of a cleft palate are manifestations of other DAs. None of the members of this kindred demonstrated these traits. Five members of this kindred demonstrate a diminished ability to fully open the mouth. This finding did not cause any functional limitation although access for dental care was more restricted. This is most notably a characteristic of DA2 (Freeman-Sheldon syndrome; FSS) and D7 (trismus-pseudocamptodactyly syndrome). It is likely that limited opening of the mouth is a relatively nonspecific trait of different multiple congenital contracture disorders.

FSS is characterized by camptodactyly, ulnar deviation, positional foot deformities, and unusual facial findings with diminished facial movement, most notably a small pursed mouth with trismus [Freeman and Sheldon 1938; Carey et al. 1993]. Hall et al. [1982] reclassified two families reported by Jorgenson [1974], and Carey et al. [1993] and Bamshad et al. [1994] reclassified a third family reported as FSS to DA1B. Furthermore, Klemp and Hall [1995] recently reported a Maori kindred with individuals exhibiting characteristics of DA1 and FSS. This suggests that allelic heterogeneity could explain the similarities between FSS and the distal arthrogryposes, especially DA1. No FSS families tested to date map to the *DA-1A* locus (Bamshad, unpublished data).

The gene causing DA1A in this kindred was recently mapped to a 65 cm pericentromeric region of chromosome 9 [Bamshad et al., 1994], and the locus has been designated *DA-1A*. Additional families map to the same locus (Bamshad, unpublished data). Yet more than 10 other DA1 families do not map to the same region, suggesting at least one other DA1 locus may exist in the genome. Current efforts are focused on narrowing the genetic region in which *DA-1A* must exist as well as testing phenotypically similar disorders. If markers closely linked to *DA-1A* can be identified, an accurate prenatal diagnostic test could be developed.

As the range of variation of the DA disorders expands, it is becoming apparent that classification of the DAs into discrete conditions based solely on their clinical findings may be error-prone. Classification of the distal arthrogryposes on the basis of biological characteristics such as the location of the disease-causing gene and/or the mechanisms producing contractures could help to resolve the relationships between disorders. Additionally, it will enable clinicians to make more precise diagnoses, improve management efficiency and more accurately predict long-term sequelae. Eventually, cloning and characterization of the DA genes will facilitate the understanding of the molecular basis of multiple congenital contracture disorders. This will be a substantial advance toward elucidating the mechanisms that alter normal development and produce congenital contractures.

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